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Letter to the Editor

Imprinting Is Also a Mechanism for Immediate or Delayed Hemizygous Expression of Several Uniparental Haplotypes Selected From the Genome of Each Sex

A peculiar and interesting aspect of monoallelic or hemizygous expression, resulting from genomic imprinting, should be a likeness or resemblance for some phenotypic traits between relatives inheriting identical active genes or domains. Although the word "likon," a neologism, is reminiscent of the above implication, it is here proposed for use in a broader sense, namely, to designate a haplotype or part of a haplotype of an imprinted domain.

As learned from earlier studies of imprinting and uniparental disomies, haplotypes at loci of such domains may be expressed (E) or unexpressed (U) in somatic cells; they may also be transmitted to be expressed or not in the next generation by germ cells "acting" (A) or marked to be "resting" (R) for such loci. Thus the soma/germinal status of "likons" might for each genitor be abbreviated as EA, UA, ER, and UR.

In an evolutionary sense the assumption is that the same monoallelically expressed loci and domains when carried by two or more relatives should be the source of identical transcripts contributing to a closely similar phenotype. If so, the overall phenotype would be distinct if arising from some 10 to 20 imprinted genes or domains potentially gaining expression from the germ cells of either one or the other sex in humans. The result may have evolutionary implications by narrowing the scope of random individual variation and by strengthening assortative and associative values (physical, behavioral, and instinctual) in one's own lineage and species. Am. J. Med. Genet. 70:95-98, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

The mouse, with a diploid chromosome number of 40, has six imprinted chromosomes, carrying some ten epigenetically modified domains responsible for 15 different phenotypes [Cattanach and Jones, 1994]. Attempts are being made at developing an imprinting map in the human [Ledbetter and Engel, 1995], which already in its preliminary stages points to striking epigenetic homologies with its rodent counterpart as apparent from studies in uniparental disomy [Engel, 1980; Ledbetter and Engel, 1995].

Genes or gene sequences that are imprinted have been subjected to epigenetic modifications characteristic of the parental sex-of-origin. This mechanism causes a bias of transmission by "singling out" genes for monoallelic expression, at loci which often influence growth and development [Driscoll, 1994; Hendrich and Willard, 1995; Sapienza and Hall, 1995].

Of the ten or so imprinted genes of the mouse currently known [Engel, 1995; Ledbetter and Engel, 1995], seven are paternally and three maternally expressed. In the human, some understanding of both the epigenetic regulation and cellular function has been obtained for only five of the mouse homologues, one of which (IGF2R) has acquired biparental expression in our species [Kalscheuer et al., 1993]. Three others are SNRPN (the gene for the small nuclear ribonucleoprotein-associated polypeptide N, a developmentally regulated spliceosome component chiefly expressed in neuronal cells where it appears to affect the splicing of neurone-specific messages [Schmaus et al., 1992; Wevrick et al., 1994]); IGF2 (the insulin-like growth factor II gene, an autocrine growth factor [DeChiara et al., 1991; Giannoukakis et al., 1993]); and H19, whose RNA transcript may be the active product, thereby belonging to a group of RNA polymerase II transcription

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units [Brannan et al., 1990]. The fifth one, Xist, the X-inactive specific RNA transcript, is peculiar. It is likely to be the regulatory switch locus that controls X chromosome hemizygous expression [Graeme et al., 1996]. Its intriguing role aims at ensuring gene dosage compensation between sexes, while causing a bias for selective paternal X hemizygous expression for some cells of the female organism.

Other human genes whose mouse homologues are imprinted are INS, MASH2, Mas, ZnF127, and U2afl-rs1 [Ledbetter and Engel, 1995]. Among the latter, MASH2 deserves special mention. In the mouse it encodes a transcription factor of the basic-helix-loop-helix class, maternally active and highly expressed in trophoblast and early embryos, and physically linked to the imprinting domain, which also includes H19, IGF2, and INS2 [Guillemot et al., 1995]. Its role in the developing human embryo awaits further clarification, as does that of a recently described new human IPW locus [Wevrick et al., 1994].

CHROMOSOME DOMAINS

Recent studies tend to indicate that imprinting involves chromosome domains, each possibly influenced by an imprinting center [Buiting et al., 1995], which may alter gene expression in the offspring by regulating the chromatin state, the replication timing, and the molecular makeup (chiefly by DNA methylation) of the areas concerned [Driscoll, 1994].

Thus, the various imprinted domains represent coordinated, uniparentally functioning units that have apparently evolved over many generations. They must therefore contain information and messages of selectively tested biological "value." The specific, and presumably polymorphic transcripts of these special domains, while expressed from one parent in the next generation when received from an active germ cell domain, are also deferred in expression when passed down to successive generations by the other sex germ cells where the domain is inactivated.

Imprinting of perhaps as many as 10 or 20 singly expressed haploid segments seems to foster the chances that an offspring will selectively reproduce some aspects of the phenotype of one parent only. As a result the chances of obvious likeness and identity to one genitor are increased since they escape inherent interplay with transcribed and translated homologous genes of the other parent. In turn, the strengthening of intrafamilial and intergenerational resemblance may have a survival value in wild-type populations.

How much of this may be true in the more immediate family can be appreciated as follows. A progenitor may transmit to each offspring a haplotype which, barring crossing over, is the one already expressed in his or her cells (a 1 in 2 probability) or (s)he can, with the same probability, transmit the haplotype, which, although unexpressed in his or her cells, was active in the progenitor's parent of the other sex. However, the inherited pattern could become liable to greater individual variation, if both haplotypes of an imprinted domain were "hot spots" of meiotic recombination, as argued in some instances [Robinson and Lalande, 1995]. To emphasize these particular aspects, I have proposed to call "likons"[1] the haplotype of an imprinted domain. The word points to the fact that the same occurs when relatives are endowed with an identical uniparentally functioning genomic part of an imprinted domain. Of course, dominant alleles, with precedence over the recessive ones of a pair, also make for expression of resemblance among individuals, related or not. The same mutation in FGFR3 at 4p16.3 causes achondroplasia [Rousseau et al., 1994] in father and son and makes them look alike, even more so. However, in a phylogenetic sense, by bearing the "seal" of imprinting, genes and gene sequences are singled out from all others, some of which are already known to play an important physiologic role in morphogenesis, neurologic function, and cell regulation, often in relation to growth and development. Epigenetic modifications in ruling out the expression of the other parent's gene are therefore at variance with other biallelic systems that bring about biparental effects as best exemplified by codominance.

EXPRESSED OR ACTING

But the message of a "likon" from one generation to the next is not necessarily analogous to the writing of a word or sentence with the same ink, from the same pen, with the same maternal or paternal hand. In a broader sense, "likons" are functionally coordinated (co-adapted) haplotypes of distinctive behavior. Their function is a result of two major attributes, namely, 1) expressed versus repressed and 2) acting versus resting.

The first two adjectives allude to their phenotype, representing expression (or not) in somatic cells. The latter two refer to their mature germinal potential: acting, that is able to code in the next generation, or resting, and marked to stay idle in the next generation. Of course, the germinal status depends on the sex of the transmitting parent and the phenotypic character. For example, the PWS-AS domain covers a 3–4 Mb area [Mutirangura et al., 1993] in the q11-13 region of chromosome 15. Its complex function apparently results from the regulation of an imprinting center [Buiting et al., 1995; Saitoh et al., 1995]. In this area, a maternal "likon," AS, is expressed in offspring, daughter or son, since it is the female sex that keeps it germinally acting. Besides, as described earlier, the same AS "likon" may then be expressed in mother and child (Fig. 1) or the "likon" may be expressed in the child from the mother's other haplotype (Fig. 2), repressed in her, but present in her father (i.e., the child's grandfather) with a 1 in 2 chance of identical expression in both.

By contrast, the part of 15q11-13 involving the PW cluster is kept active in the father and, thus, the so-called PWS "likon" is expressed and acts paternally (with 0.5 chance of transmission to offspring).

[1]This material (including the term "likon") was presented in part at the Third International Symposium on "Genetics, Health, and Disease," Amritsar, India, December 1–4, 1995, and at the Workshop "From Chromosome to Gene," Fondazione Centro Auxologico Italiano, Milano, Italy, April 29, 1996.

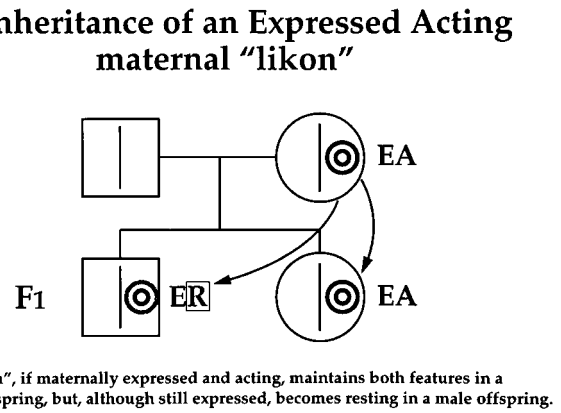

Fig. 1. In this example a maternally expressed (E, inner circle) and germinally acting (A, outer circle) "likon" segregates in a daughter, unchanged (EA), and in a son, where, although expressed, it becomes germinally resting (ER).

A "likon" can be mutated in various ways in its different coordinated parts. In PWS, no less than four such processes might be considered: an expressed and/or acting "likon" could be lost through paternal deletion [Ledbetter et al., 1981] or maternal disomy [Nicholls et al., 1989; Toth-Fejel et al., 1996]; it could be mutant (even point mutated) in one at least of several intrinsic regulated genes such as SNRPN [Sun et al., 1996], possibly causing an only partial phenotype [Cassidy et al., 1993]. It could also mutate in its regulatory function causing methylation imprinting defects [Buiting et al., 1995; Saitoh et al., 1995]. Thus, in both AS and PWS particularly in familial cases, minimal deletions, a few kb, in the presumed cis acting area of the imprinting center (between PW71B and SNRPN) can, in the germ cells, put to rest a "likon" which, in essence, should have been passed acting to an offspring from the parent of the proper gender. When silenced by such mutations or deletions, loci of the paternal "likons" (ZnF127, PW71B, and SNRPN exon α among them) acquire the same epigenetic methylation pattern as if it were the normally repressed maternal one [Reis et al., 1994].

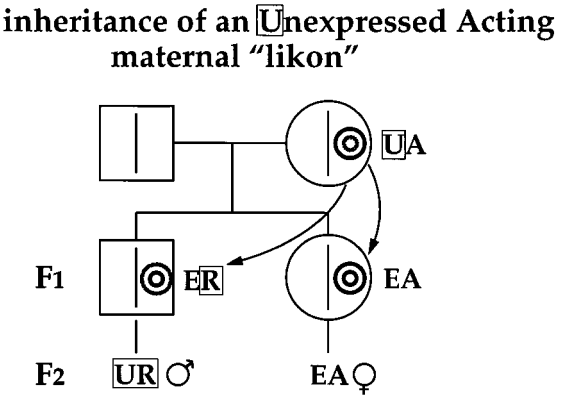

Fig. 2. An unexpressed (U) maternally acting (A) "likon" is expressed (E) and acting (A) when transferred to a daughter, to remain so as long as it is passed down to female offspring. Also expressed (E) in an F1 male, it becomes resting (R) in its germ cells to become both unexpressed and resting (UR) as long as it segregates in succeeding male generations.

It is of interest that imprinted genes cluster in larger, coordinated, regulated domains [Saitoh et al., 1995] of contrasting parent-of-origin activity as exemplified by H19 and IGF2 in humans, with H19 maternally expressed (acting) and IGF2 paternally expressed [Moulton et al., 1994; Steenman et al., 1994]. Consequently, H19 and IGF2 are "likons" of differential parental function. Maternal "likon" reversal (i.e., IGF2 expressed, H19 repressed) have been shown to play a part in Wilms tumor–Wiedemann-Beckwith syndrome possibly through "enhancer competition" [Moulton et al., 1994; Rainier et al., 1993; Steenman et al., 1994]. In like manner, a breakpoint at 11p15.5 [Tommerup et al., 1993; Engel, 1995] in familial cases may render the maternal IGF2 "likon" germinally acting, thereby gaining expression in her offspring along with the normally expressed paternal one and causing functional imbalance.

OTHER REGIONS

Current knowledge of imprinting regions in humans [Ledbetter and Engel, 1995] suggests a pat 7q "likon" whose absence most obviously causes short stature [Eggerding et al., 1994; Kotzot et al., 1995]. Others on 11p15.5 have been alluded to [Henry et al., 1991]. There exists one in both maternal and paternal 14 [Antonarakis et al., 1993; Ledbetter and Engel, 1995; Engel, 1995] whose defect can cause malformation syndromes, just as has been seen in maternal and paternal 15.

The proposed term then points to the underlying unique homologies, both genotypic and phenotypic that must result from the same repetitious uniparental hemizygous transfer of expression among relatives.

Coining a word and defining it must serve understanding among scientists and clinicians [Engel, 1997]. In this proposed instance, one might find it easier to refer to, say, "likon" 15q11-13 AS or PWS (maternal or paternal) than to the 15q11-13 AS segment that is paternally imprinted and transmitted actively from the mother, and vice versa. Here, a few single words, maternally expressed and acting AS "likon," suffice to provide full information while also indicating that we are dealing with an imprinted system.

An attempt is also made at pointing to a possible "teleological" facet of imprinting, which is responsible for a non-Mendelian transmission bias, one which also vastly transcends the mammalian reign and uses many different biological vehicles to impose itself [Hendrich and Willard, 1995]. Its ultimate purpose and means of implementation often remain mysterious [Hendrich and Willard, 1995; Sapienza and Hall, 1995]. Its short-term adaptive value was discussed recently by Pembrey [1995]. One of its adaptive values might also be to maintain the assortative traits of a species, physical, behavioral, and instinctual, by narrowing the scope of random variation in one's own lineage.

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